# Perspective on the "Animal Rule"

Karen L. Goldenthal, M.D.
OVRR/CBER

# Efficacy Issues for Counter Terrorism (CT) Products

- In some cases, human efficacy trials may not be feasible nor ethical
  - ☑ Epidemiology precludes “field trials”, the usual source of efficacy data, and
  - ☑ Cannot conduct human challenge/protection studies

# Animal Rule

- **New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. Federal Register 67: 37988-37998, May 31, 2002. (Final Rule)**
  - ☑ **21 CFR 601.90-95 (biologicals)**
  - ☑ **21 CFR 314.600-650 (drugs)**

# Animal Rule

- **Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances**

# Animal Rule

- FDA may approve a product for which
  - ☑ Safety has been established and
  - ☑ Requirements of Sec. 601.90 (314.600) met based on adequate and well-controlled animal trials when results of those animal studies establish that product reasonably likely to provide clinical benefit in humans

# Animal Rule

- **Rely on evidence from animal studies only where**
  - ☑ **Reasonably well understood**
    - **Mechanism of toxicity of agent**
    - **How product prevents the toxicity**
  - ☑ **Effect independently substantiated in >1 species (some exceptions)**
    - **Including species expected to react with a response predictive for humans**

# Animal Rule

- **Animal study endpoint clearly related to desired benefit in humans**
  - ☑ **Generally, enhancement of survival or prevention of major morbidity**
- **Selection of an effective dose in humans**
  - ☑ **Kinetics & pharmacodynamics and/or other relevant data, in animals & humans**
- **Still need human clinical data**
  - ☑ **Safety**
  - ☑ **PK/immunogenicity data**

# Animal Rule

## Approval subject to three requirements

- **Postmarketing (PM) studies**
  - ☑ To verify and describe the product's clinical benefit when feasible & ethical (due diligence)
  - ☑ May not be feasible until an exigency arises
- **PM restrictions as needed to assure safe use, commensurate w/product specific safety concerns**
  - ☑ E.g., distribution restricted to certain facilities or health care providers with special training or experience, if needed

# Animal Rule

*Continued*

**Approval subject to three requirements**

- **Labeling for recipients**
  - ☑ **Provided prior to use**
  - ☑ **Explain that product's approval based on efficacy studies conducted in animals alone**
  - ☑ **Indication(s)**
  - ☑ **Directions for use (dosage & administration)**
  - ☑ **Contraindications**
  - ☑ **Adverse Events**
  - ☑ **Other relevant information**

# Animal Rule

- **Reasons to withdraw approval**
  - ☑ **PM clinical study fails to verify clinical benefit**
  - ☑ **Applicant fails to perform PM study with due diligence**
  - ☑ **Experience shows that PM restrictions are inadequate to ensure safe use of the product**
  - ☑ **Applicant fails to adhere to PM restrictions**
  - ☑ **Promotional materials false or misleading, or**
  - ☑ **Other evidence demonstrates that product is not safe or effective**

# Animal Rule - Scope

- **Rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations**
  - ☑ **e.g., accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity**

# Safety Data

## Indication: Preventive vaccines for healthy persons

- Target populations
- How much is enough to support licensure?
- Thousands, ideally from randomized studies
- Data quality important
- Risk/benefit

# Safety Evaluation

- Animal rule does not address safety evaluation of products to which it applies
- Safety discussed briefly in preamble to Rule
  - ☑ Use "preexisting requirements"
- Agency believes that, w/one limitation, safety of most of these products can be studied in volunteers similar to people who would be exposed to the product
- Limitation – may be inability to examine possible adverse interactions between toxic substance and new product

# "Supplemental Clinical Studies" To Assess Safety (Prelicensure)

- **Small efficacy trials or other limitations**
  - ☑ **E.g., if efficacy assessed by comparative immunogenicity study(s) with several hundred per group (combination vaccines)**
  - ☑ **"Animal rule"**
- **Novel vaccine concepts**

# Simultaneous Administration (SA)

- FDA's Guidance for Industry for Evaluation of Combination Vaccines (1997)
- Note: No previous FDA policy on this topic
- Licensed vaccines administered simultaneously w/the new vaccine:
  - ☑ Obtain immunogenicity & safety data to support SA if recommended schedule for new vaccine is same, or overlaps, with one or more licensed vaccines
  - ☑ Timing: Prelicensure

# Standards of Licensure

- Safety
- Purity
- Potency
- Efficacy
- Stability
- cGMP Compliance

# Vaccine Production/Quality Control

## Common Principles

- Detailed manufacturing procedures: consistency of production
- Defined compatible components
- Product characterization: specifications
- Cell substrate; Adventititous agent testing
- Source (e.g., BSE)
- Examination for extraneous materials
- Stability

Baylor NW and Midthun K. Regulation and testing of vaccines. In: Plotkin SA and Orenstein WA (eds.), *Vaccines*, 4th ed., 2004.

# Implications of Proposed Rule for Drug Development

- Early/multiple discussions with FDA
- Detailed justification concerning why efficacy trials not feasible/ethical
  - ☑ Agency may not concur
  - ☑ Ability to perform "field trials" may change over time, e.g.,
    - Clinical endpoint efficacy trial for anthrax vaccine possible in 1950s/60s (US mill workers)*

*Brachman, et. al., 1962. Field evaluation of a human anthrax vaccine. Am J Public Health. 52:632-645

# Implications - Drug Development

- Pilot efficacy studies in animals
- Pivotal animal efficacy studies
  - ☑ Prospective primary endpoint
  - ☑ Prospective statistical plan
  - ☑ GLP (21 CFR 58)
- Multiple interactions with FDA Advisory Committees
  - ☑ Prior to animal efficacy trials, for concurrence w/concepts, in some cases
  - ☑ Following Agency's BLA review

# Assays in Vaccine Trials

**Importance of:**

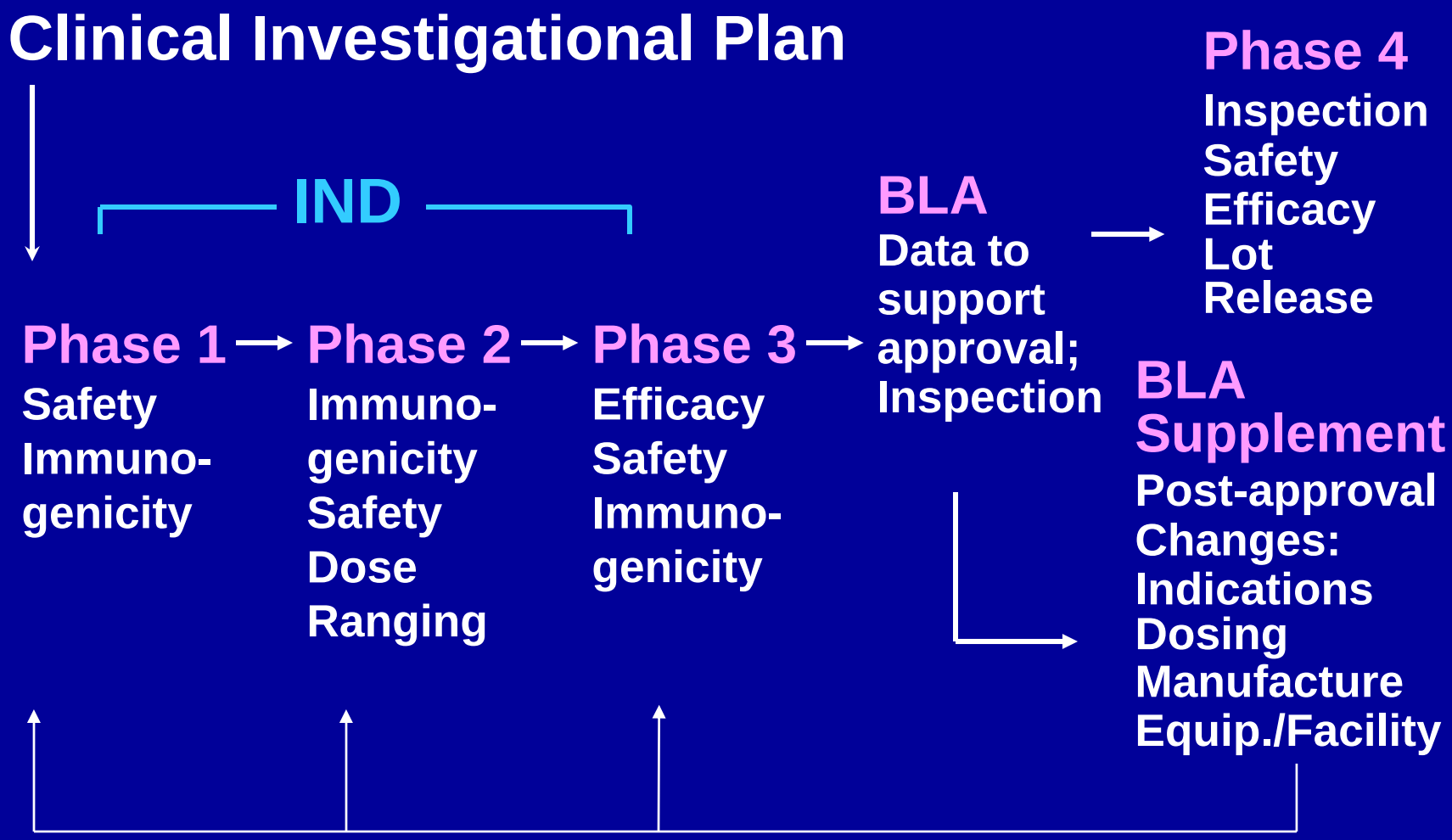
- **Assays to detect vaccine-elicited response(s)**
- **Assays to identify/characterize infections (immunologic, virologic)**
- **Considerable R & D can be necessary to develop and validate assays**

# Assays in Vaccine Trials

**Importance of:**

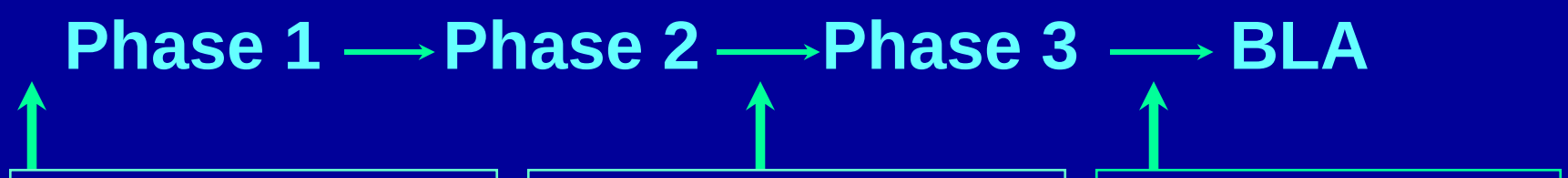
- **Assay performance data**
  - ☑**Specificity, sensitivity, ruggedness, reproducibility, e.g., procedures to minimize false positive PCR**
  - ☑**Important for early trials**
  - ☑**Validation of assays before pivotal study**

# Stages of Review and Regulation




IND =Investigational New Drug Application; BLA=Biologics License Application

# Meetings with FDA (21 CFR 312.47)




**Pre-IND Meeting:**

- Manufacturing
- Product
- Lot Release
- Animal safety & immunogenicity
- Phase 1 protocol

**End-of-Phase 2 Meeting:**

- Efficacy trial protocol(s)
- Phase 1/2 data
- Update** Product, etc.
- Rationale

**Pre-BLA Meeting:**

- Clinical data summary: S & E
- Update** Product, etc.
- Outline of BLA

BLA = Biologics License Application **Shouldn't be a surprise

# Available Resources

## Example of an FDA document:

- ☑ Guidance for industry - Content & format of chemistry, manufacturing & controls information & establishment description information for a vaccine or related product (1999)

# Available Resources

- FDA documents/Federal Register notices/regulations
  - ☑ http://www.fda.gov/cber/publications.htm
  - ☑ 1-800-835-4709 or 301-827-1800
- International Conference on Harmonisation (ICH) documents
  - ☑ U.S., E.U. and Japan
- Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop - 4/23/2002 – Transcript on CBER internet

# Conclusion - Product Development

- CT products present unique issues for clinical development
- Overall planning and coordination:
  - ☑ Product characterization/manufacturing
  - ☑ Early/frequent interaction with Agency, esp. if approval will be based on animal efficacy data
  - ☑ Anticipate future trials (e.g., critical assays)
  - ☑ Obtain sufficient safety, immunogenicity & efficacy data during development
- Utilize FDA documents & resources